Remnant cholesterol as a cause of ischemic heart disease: Evidence, definition, measurement, atherogenicity, high risk patients, and present and future treatment

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Abstract

This review focuses on remnant cholesterol as a causal risk factor for ischemic heart disease (IHD), on its definition, measurement, atherogenicity, and levels in high risk patient groups; in addition, present and future pharmacological approaches to lowering remnant cholesterol levels are considered. Observational studies show association between elevated levels of remnant cholesterol and increased risk of cardiovascular disease, even when remnant cholesterol levels are defined, measured, or calculated in different ways. In-vitro and animal studies also support the contention that elevated levels of remnant cholesterol may cause atherosclerosis same way as elevated levels of low-density lipoprotein (LDL) cholesterol, by cholesterol accumulation in the arterial wall. Genetic studies of variants associated with elevated remnant cholesterol levels show that an increment of 1 mmol/L (39 mg/dL) in levels of nonfasting remnant cholesterol associates with a 2.8-fold increased risk of IHD, independently of high-density lipoprotein cholesterol levels. Results from genetic studies also show that elevated levels of remnant cholesterol are causally associated with both low-grade inflammation and IHD. However, elevated levels of LDL cholesterol are associated with IHD, but not with low-grade inflammation. Such results indicate that elevated LDL cholesterol levels cause atherosclerosis without a major inflammatory component, whereas an inflammatory component of atherosclerosis is driven by elevated remnant cholesterol levels. Post-hoc subgroup analyses of randomized trials using fibrates in individuals with elevated triglyceride levels, elevated remnant cholesterol levels, show a benefit of lowering triglycerides or remnant cholesterol levels; however, large randomized trials with the primary target of lowering remnant cholesterol levels are still missing.

Keywords:
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Contents

1. Introduction including definition ........................................ 359
2. Remnant cholesterol levels and observational risk of ischemic heart disease ........................................ 359
3. Remnant cholesterol, genetic variation, and causal risk of ischemic heart disease ........................................ 360
4. Measurement of remnant cholesterol ........................................ 361
5. Atherogenicity of elevated remnant cholesterol ........................................ 361
6. Remnant cholesterol levels in high risk patient groups ........................................ 362
7. Lowering of remnant cholesterol levels using current approaches ........................................ 364
8. Future pharmacological approaches to lowering remnant cholesterol levels ........................................ 364
9. Conclusions and perspectives ........................................ 365

Abbreviations:
HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; IHD, ischemic heart disease; LDL, low-density lipoprotein; LRP, LDL receptor-related protein; VLDL, very-low-density lipoprotein.

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1. Introduction including definition

Ischemic heart disease (IHD) is a leading cause of morbidity and mortality worldwide. An important risk factor for IHD is elevated levels of low-density lipoprotein (LDL) cholesterol, but even after lowering of LDL cholesterol to recommended levels, there is a considerable residual risk of IHD. Some of this residual risk may be explained by elevated remnant cholesterol levels (Chapman et al., 2011).

Lipoproteins transport water-insoluble triglycerides and cholesterol between tissues and organs in the body (Havel & Kane, 2001). They consist of a core of hydrophobic cholesterol esters and triglycerides surrounded by a hydrophilic mono-layer of phospholipids, free cholesterol, and apolipoproteins. The different classes of lipoproteins, i.e. chylomicrons, chylomicron remnants, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL, lipoprotein(a) and high-density lipoprotein (HDL), are different in density as a result of the amount of triglycerides and cholesterol they contain, and have different apolipoproteins on their surface. Chylomicrons, chylomicron remnants, VLDL, and IDL are rich in both triglycerides and cholesterol and have relatively low densities, whereas LDL, lipoprotein(a), and HDL mainly contain cholesterol and have a higher density. Lipoproteins are produced by two pathways: 1) the endogenous pathway in which VLDL are assembled in hepatocytes and are converted to IDL and LDL by triglyceride lipolysis in plasma (on the luminal surface of endothelial cells lining the capillaries or in the lumen of vessels) and by exchange of lipids and apolipoproteins with other lipoproteins, and 2) the exogenous pathway in which chylomicrons are produced by enterocytes, and are converted to chylomicron remnants by triglyceride lipolysis in plasma (Havel & Kane, 2001). Finally, lipoprotein(a) is an LDL particle with an additional apolipoprotein(a) attached, and levels of this lipoprotein is mainly genetically determined (Nordestgaard et al., 2010; Kronenberg & Utermann, 2013).

After secretion of chylomicrons from the intestine and VLDL from the liver, both types of lipoproteins are enriched in apolipoprotein E during their degradation to remnants. Apolipoprotein E is important for the uptake of remnants by the liver, because it, like apolipoprotein B, functions as a ligand for hepatic receptors, i.e. the LDL and LRP (LDL receptor-related protein) receptors (Havel, 2010; Ramasamy, 2013). Consequently, mutations in the APOE gene can cause increased plasma levels of cholesterol and triglycerides (Frikk-Schmidt et al., 2000). However, hepatic uptake of remnants is complex and not fully understood, and mechanisms other than uptake via the LDL and LRP receptors have been proposed, such as internalization after binding to heparan sulfate proteoglycans (MacArthur et al., 2007).

We define remnant cholesterol as the cholesterol content of a subset of the triglyceride-rich lipoproteins called remnants, i.e. chylomicron remnants, VLDL, and IDL in the nonfasting state, and VLDL and IDL in the fasting state; in most individuals chylomicrons are not present in plasma as these particles are degraded to chylomicron remnants very fast due to rapid triglyceride hydrolysis by lipoprotein lipase. Remnant cholesterol levels are therefore highly correlated with triglyceride levels (Varbo et al., 2013a). In plasma, triglycerides and cholesterol are exchanged between HDL and remnants, and levels of HDL cholesterol and remnant cholesterol are inversely correlated. This has previously made it difficult to determine if it is low levels of HDL cholesterol per se or the concurrent high levels of remnant cholesterol and triglycerides per se is the cause of the increased risk of IHD found in observational studies.

The aim of this review is first to summarize current evidence of elevated levels of remnant cholesterol as a causal risk factor for IHD including results from observational studies, experimental studies, genetic studies, and randomized clinical intervention trials. Second, we describe measurement of remnants, the pathophysiology behind the atherogenicity of remnants, and presence of elevated remnant cholesterol levels in high risk patient groups. Finally, we review present and future pharmacological approaches to lowering remnant cholesterol levels.

2. Remnant cholesterol levels and observational risk of ischemic heart disease

Large observational studies, and meta-analyses thereof, have shown that elevated triglycerides are associated with increased risk of cardiovascular disease (Austin, 1991; Hokanson & Austin, 1996; Nordestgaard et al., 2007; Freiberg et al., 2008; Di Angelantonio et al., 2009; Chapman et al., 2011; Varbo et al., 2011b); however, the association of elevated remnant cholesterol levels with cardiovascular disease risk is not as thoroughly studied. Although there has been many studies of the association of remnant cholesterol levels with cardiovascular disease, most have been relatively small case-control studies (Devaraj et al., 1998; Sakata et al., 1998; Kugiyama et al., 1999; Takeichi et al., 1999; Masuoka et al., 1998, 2000a, 2000b; Song et al., 2000; Higashi et al., 2001; Karpe et al., 2001; Inoue et al., 2004; Miwa et al., 2004; Oi et al., 2004; Hopkins et al., 2005; Lamon-Fava et al., 2008; Hiki et al., 2009) or observational studies (McNamara et al., 2001; Fukushima et al., 2001, 2004; Imke et al., 2005; Nakamura et al., 2005) using different assays (and thereby definitions) for determining remnant cholesterol levels. Most of the studies measured remnant cholesterol in the fasting state; however, studies of triglyceride levels, which are highly correlated with remnant cholesterol levels (Fig. 1), have shown that elevated nonfasting levels of triglycerides are consistently associated with increased risk of cardiovascular disease, and are possibly more useful for predicting risk of cardiovascular disease than fasting levels of triglycerides (Bansal et al., 2007; Freiberg et al., 2008; Mora et al., 2008; Stalenhoef & de Graaf, 2008; Nordestgaard et al., 2007, 2009; Kolovou et al., 2011; Langsted et al., 2011; Nordestgaard & Freiberg, 2011; Varbo et al., 2011b).

![Fig. 1. Lipoprotein cholesterol as a function of increasing levels of nonfasting triglycerides. Data are from the Copenhagen General Population Study. R^2 = 0.96 for the correlation of remnant cholesterol levels with triglyceride levels. HDL = high-density lipoprotein, LDL = low-density lipoprotein. Modified from Varbo et al. J Am Coll Cardiol 2013;61:427–436.](image-url)
Most people are in the nonfasting state most of the day, since fasting implies not eating for at least 8 h, and for most people in affluent countries this is only the case early in the morning. This argues for examining association of remnant cholesterol levels with cardiovascular disease in the nonfasting state. We previously reported an association of elevated nonfasting remnant cholesterol levels, calculated as nonfasting total cholesterol minus HDL cholesterol minus LDL cholesterol, with increased risk of IHD in a large sample of the general population (Varbo et al., 2013a). Individuals with nonfasting remnant cholesterol levels in the upper fifth quintile, that is, remnant cholesterol levels >1.1 mmol/L (≥43 mg/dL), had a hazard ratio for IHD of 2.3 (95% confidence interval: 1.7–3.1) compared to individuals with nonfasting remnant cholesterol levels in the lowest quintile, that is, <0.4 mmol/L (<16 mg/dL) (Fig. 2, top panel). Similarly, the ratio of nonfasting remnant cholesterol to HDL cholesterol was also significantly associated with increased risk of IHD, with a hazard ratio of 2.6 (2.3–3.2) for a ratio >0.8 compared to a ratio <0.2 (Fig. 2, upper middle panel). In that study, elevated levels of nonfasting remnant cholesterol and increased ratio of nonfasting remnant cholesterol to HDL cholesterol associated with increased risk of IHD in a magnitude similar to those seen for elevated LDL cholesterol and reduced HDL cholesterol levels (Fig. 2, lower and lower middle panel), both of which are well-known markers of increased risk of cardiovascular disease.

3. Remnant cholesterol, genetic variation, and causal risk of ischemic heart disease

Plasma levels of remnant cholesterol (and likewise triglycerides) are partly genetically determined by common and rare genetic variants (Yuan et al., 2007; Hegele et al., 2009; Johansen et al., 2011a, 2011b), and partly determined by lifestyle factors such as diet, obesity, alcohol intake, and physical activity (Chapman et al., 2011). Several rare genetic variants are known to influence levels of triglycerides, and thus remnant cholesterol levels, such as deleterious mutations in the LPL, APOC2, APOA5, LMF1, and GPIHBP1 genes that in homozygote or compound heterozygote forms can cause severe chylomicronemia (Brunzell & Deeb, 2001; Johansen & Hegele, 2011). However, there are also numerous common genetic variants that influence levels of remnant cholesterol, but with a smaller effect size than the rare genetic variants. Many of the common variants have been indentified in genome wide association studies (GWAS) aimed at identifying genetic variants associated with levels of triglycerides (Kathiresan et al., 2008; Willer et al., 2008; Teslovich et al., 2010). Associations of some of these common genetic variants with lipoprotein levels were replicated in large general population studies by us (Varbo et al., 2011a; Jorgensen et al., 2013), which showed that variants in TRIB1 (rs2954029), GCKR (rs1260326), and three variants in APOA5 (rs651821, rs3135506, and rs619054) were associated with higher levels of nonfasting triglycerides, remnant cholesterol, and LDL cholesterol, and with lower levels of HDL cholesterol, and also that the TRIB1 and APOA5 variants were associated with increased risk of IHD and myocardial infarction; however, the GCKR variant was not associated with risk of IHD or myocardial infarction. TRIB1 encodes tribble-1 which is a protein with a regulatory effect on mitogen-activated protein kinase (Kiss-Toth et al., 2004), and TRIB1 is an example of a gene identified in GWAS that was previously not known to be involved in atherosclerosis development.

In the metabolism of lipoproteins, the cholesteryl ester transfer protein (CETP) exchange triglycerides for cholesterol esters between...
remnants and HDL particles, leading to inversely correlated levels of remnant cholesterol and HDL cholesterol (Fig. 1). Therefore, most genetic variants that are associated with elevated levels of remnant cholesterol are also associated with low levels of HDL cholesterol, and to some extent also with elevated LDL cholesterol levels. This has previously made it difficult to separately determine the causality of elevated levels of remnant cholesterol and low levels of HDL cholesterol on risk of IHD. To circumvent this, we conducted a Mendelian randomization study on 73,513 participants from three Danish studies (Varbo et al., 2013a), in which we used 15 genetic variants combined into four allele scores that affected levels of either 1) nonfasting remnant cholesterol alone, 2) remnant cholesterol and HDL cholesterol combined, 3) HDL cholesterol alone, and as a positive control 4) LDL cholesterol alone (Fig. 3). In that study, we found the group of genetic variants affecting only remnant cholesterol levels, and the group of genetic variants affecting both remnant cholesterol and HDL cholesterol levels, to be causally associated with IHD, with a causal odds ratio of 2.8 (1.9–4.2) per 1 mmol/L (39 mg/dL) higher level of remnant cholesterol and a causal odds ratio of 2.9 (1.9–4.6) for a 1 ratio increase of remnant cholesterol to HDL cholesterol, respectively (Fig. 4). However, the group of genetic variants that only affected levels of HDL cholesterol was not causally associated with risk of IHD. From this, we concluded that elevated levels of remnant cholesterol cause IHD, independently of HDL cholesterol levels.

4. Measurement of remnant cholesterol

Separation of lipoproteins into different classes was first done by ultracentrifugation in the 1940’s (Gofman et al., 1956). Since then, assays for measuring remnants using different methods have been developed (Havel, 2000; Nakajima et al., 1993, 2011; Ooi & Nordestgaard, 2011; Hanada et al., 2012). However, as lipoprotein remnants are different both in composition of lipids and apolipoproteins as a result of different stages of triglyceride lipolysis and exchange of apolipoproteins and lipids with other lipoproteins, and also because remnants are formed by two different pathways, i.e. the endogenous and the exogenous pathways, it is difficult to create an assay that measures all remnants at the same time (Ooi & Nordestgaard, 2011). An alternative to directly measuring remnants is to calculate nonfasting remnant cholesterol levels as nonfasting total cholesterol minus HDL cholesterol minus LDL cholesterol, like it has been done in several studies of large Danish cohorts (Nordestgaard et al., 2007; Freiberg et al., 2008; Varbo et al., 2011a; Varbo et al., 2011b; Jorgensen et al., 2013; Varbo et al., 2013a; Varbo et al., 2013b). Although possibly not as precise as directly measuring remnants, the advantage of calculating remnant cholesterol is that it is simple and straightforward, that is, that remnant cholesterol, like LDL cholesterol, enter and is trapped in the intima of the arterial wall (Shaikh et al., 1991; Nordestgaard et al., 1992; Nordestgaard et al., 1995), leading to accumulation of intimal cholesterol, atherosclerosis and ultimately IHD (Fig. 5).

Different sizes of lipoproteins presumably play a role in their ability to enter the arterial wall and get trapped. Studies in rabbit and in

**Fig. 3.** Lipid levels as a function of genotypes in allele counts. Bars show mean lipid levels with standard error whiskers in participants from the Copenhagen General Population Study and the Copenhagen City Heart Study not using lipid lowering therapy. Genetic variants included in each group are shown in brackets. P-values for trend were estimated by Cuzick’s extension of the Wilcoxon rank sum test. HDL = high-density lipoprotein, LDL = low-density lipoprotein. Modified from Varbo et al. J Am Coll Cardiol 2013;61:427–436.
human atherosclerotic plaque tissue have shown that chylomicrons and large VLDL particles are too large to enter the arterial wall (Nordestgaard & Zilversmit, 1988; Nordestgaard et al., 1988), but that their remnants penetrate the arterial intima and get trapped in the connective tissue of the arterial wall and eventually accumulate (Shaikh et al., 1991; Nordestgaard et al., 1992; Rapp et al., 1994; Nordestgaard et al., 1995). In line with this, patients who are homozygous for rare deleterious mutations in the LPL gene, causing chylomicronemia with extremely high levels of large chylomicrons and VLDLs, have an increased risk of pancreatitis, but not an increased risk of IHD (Brunzell & Deeb, 2001). Also, in-vitro studies have shown that remnants, unlike LDL, may not need to be oxidized in order to be taken up by macrophages to cause foam cell formation and atherosclerosis (Nakajima et al., 2006).

Remnants may also be involved in the development of atherosclerosis and IHD by other pathways than by accumulation of cholesterol in the arterial wall. Experimental studies have found remnants to be associated with mechanisms underlying endothelial dysfunction, such as impaired vasodilation (Zheng & Liu, 2007) and enhanced inflammatory response (Giannattasio et al., 2005; Ting et al., 2007; Alipour et al., 2008; Wang et al., 2009; Zilversmit, 1979), and to play a role in plaque disruption and thrombus formation (Falk et al., 1995; Davies, 1996; Moyer et al., 1998; Kohler & Grant, 2000; Sambola et al., 2003; Grant, 2007). Also, our results from a large multi-directional Mendelian randomization study of 60,608 individuals with 10,668 cases of IHD indicated that elevated levels of remnant cholesterol may not cause atherosclerosis in exactly the same way as LDL cholesterol (Varbo et al., 2013b). We thus found that elevated levels of remnant cholesterol were causally associated with both low-grade inflammation and IHD; however, elevated levels of LDL cholesterol were associated causally with IHD, but not with low-grade inflammation (Fig. 6). These results were consistent even in participants without obesity and without diabetes mellitus. Such results indicate that elevated LDL cholesterol levels cause atherosclerosis without a major inflammatory component, whereas an inflammatory component of atherosclerosis is driven by elevated remnant cholesterol levels.

6. Remnant cholesterol levels in high risk patient groups

The most common cause of elevated remnant cholesterol and triglycerides is obesity (Table 1). Likewise, poorly controlled diabetes mellitus and excessive alcohol intake are common causes of elevated remnant cholesterol levels. In some women, high estrogen levels, either endogenous during pregnancy or from exogenous sources like oral contraceptives or hormone replacement therapy, can lead to high triglycerides, and possibly high remnant cholesterol levels. Kidney and liver diseases, and a number of different drugs, including oral glucocorticoids, can lead to elevated remnant cholesterol levels. Importantly, on top of these lifestyle and exogenous factors just mentioned, the genetic make-up of the individual person, including both rare and common genetic variants, determines the extent of elevated triglycerides and remnant cholesterol levels (Hegele et al., 2009; Johansen et al., 2011a; Johansen et al., 2011b).
The chylomicronemia syndrome with typically triglycerides >25 mmol/L (>2200 mg/dL) is a special case with increased risk of pancreatitis and usually normal risk of IHD (Brunzell & Deeb, 2001), unless triglycerides are lowered substantially, when the risk of IHD in these patients may still be increased (Benlian et al., 1996); importantly, the patients in the later study displayed multiple risk factors for IHD. The simple explanation for this seemingly paradox is that at very high triglyceride levels, lipoproteins are too large to enter into the arterial intima to cause atherosclerosis (Nordestgaard & Zilversmit, 1988; Nordestgaard et al., 1988), while when triglycerides are lowered...
substantially, lipoproteins become smaller and are then able to penetrate into and get trapped in the arterial wall (Shaikh et al., 1991; Nordestgaard et al., 1992; Rapp et al., 1994; Nordestgaard et al., 1995).

The classic genetic forms of the chylomicronemia syndrome are caused by homozygosity (or compound heterozygosity) for deleterious mutations in the *LPL* gene encoding lipoprotein lipase, the enzyme degrading triglycerides in plasma, or mutations in genes encoding cofactors and other proteins necessary for lipoprotein lipase function like in *APOC2*, *APOA5*, *LMF1*, and *GPIHBP1* (Brunnerz & Deeb, 2001; Johansen & Hegele, 2011). These genetic forms of the chylomicronemia syndrome are rare; however, the more commonly observed forms are caused by the interplay of genetic factors with external factors (Yuan et al., 2007; Gotoda et al., 2012), which are typically poorly controlled diabetes mellitus, excessive alcohol intake, and high estrogen levels in some women, as mentioned above.

### 7. Lowering of remnant cholesterol levels using current approaches

In a recent consensus document (Chapman et al., 2011), therapeutic targeting of triglycerides ≥1.7 mmol/L (≥150 mg/dL) was recommended in patients at high risk of cardiovascular disease after lowering of LDL cholesterol below recommended levels, which includes lowering of remnant cholesterol. Elevated levels of remnant cholesterol can be lowered by lifestyle changes and by pharmacological therapy. Lifestyle changes that effectively lower remnant cholesterol levels include weight reduction (the most important), reduced alcohol intake, reduced dietary intake of saturated fat, smoking cessation, and increased physical activity (Chapman et al., 2011). The mechanisms by which lifestyle changes reduce remnant cholesterol levels are by decreasing hepatic secretion and by increasing hepatic clearance of VLDL particles.

Current pharmacological therapy that lowers remnant cholesterol levels includes statins, niacin, and fibrates. Randomized clinical intervention trials aimed at lowering LDL cholesterol levels with statins have shown that triglycerides and non-HDL cholesterol, the latter being LDL cholesterol plus remnant cholesterol, were also lowered during treatment (Grundy et al., 2004; Gotto & Moon, 2012); however, these findings were in post-hoc analyses, and most statin trials excluded participants with triglycerides >4 mmol/L (≥350 mg/dL), making it impossible to know the potential benefit of statin treatment in those with elevated remnant cholesterol levels and triglycerides >4 mmol/L (≥350 mg/dL). There have so far not been conducted randomized clinical intervention trials with statins among patients with hypertriglyceridemia with the primary target of lowering triglyceride and/or remnant cholesterol levels.

Randomized trials with niacin in addition to statin or fibrate therapy have lead to conflicting results regarding reduction in risk of cardiovascular disease (Carlson & Rosenhamer, 1988; Lavigne & Karas, 2013). The Coronary Drug Project showed that immediate release niacin 3 g/day was associated with a 26% reduction in non-fatal myocardial infarction after 7 years of follow-up and a 11% reduced all-cause mortality after 15 years of follow-up (Canner et al., 1986; Clofibrate and niacin in coronary heart disease, 1975); however, the AIM-HIGH study found no additional effect of adding extended-release niacin in addition to statin therapy in secondary prevention of cardiovascular disease (Boden et al., 2011). Importantly, the AIM-HIGH study requested additional LDL cholesterol lowering if the LDL cholesterol target was not met, even in the niacin placebo arm, making it very difficult to show an effect of niacin added to statin treatment. Results from the HPS2-THRIVE study, examining the effect of adding niacin to statin therapy in a wider range of patients are awaited, but preliminary results show lack of effect together with substantial side effects in the niacin group (Haynes et al., 2013; HPS2-THRIVE press release on preliminary results, 2013). Concerning remnant cholesterol it should be emphasized though, that both the AIM-HIGH and the HPS2-THRIVE studies recruited very few participants with particularly elevated remnant cholesterol levels, meaning that current evidence cannot educate us about the effect of niacin when given to high risk individuals with elevated remnant cholesterol levels. The only appropriate trial for this question was the trial by Carlson & Rosenhamer in, 1988 of combined niacin and fibrate treatment given to myocardial infarction survivors (Carlson & Rosenhamer, 1988). Although this trial showed a clear 26% reduction in total mortality and a 36% reduction in IHD mortality in the treatment group, these results should be interpreted cautiously as the trial was not blinded.

Randomized clinical intervention trials examining fibrates in prevention of cardiovascular disease have also produced conflicting results, primarily showing effect on reduction of risk of non-fatal myocardial infarction, but with no effect on risk of ischemic stroke or cardiovascular mortality (Jun et al., 2010). However, these trials mainly focused on elevated LDL cholesterol levels or reduced HDL cholesterol levels, and a meta-analysis of post-hoc analyses from several fibrate trials of subgroups of patients with elevated triglyceride levels, showed a large benefit of fibrates on risk of cardiovascular disease in these patients (Sacks et al., 2010; Chapman et al., 2011).

Statins are the first choice of therapy in patients with hyperlipidemia; however, addition of fibrates or possibly niacin should be considered in patients who have hypertriglyceridemia, and thus elevated remnant cholesterol levels, despite optimal statin treatment and lifestyle interventions. Although the addition of niacin to statin therapy can be questioned after the negative results of the AIM-HIGH (Boden et al., 2011) and HPS2-THRIVE (Haynes et al., 2013; HPS2-THRIVE press release on preliminary results, 2013) studies, as mentioned above, these trials were not designed to look at effects of niacin addition to statin in those with elevated levels of remnant cholesterol.

Taken together, there is a need for large randomized clinical intervention trials investigating if reducing remnant cholesterol levels (and triglyceride levels) in patients with elevated levels will reduce the risk of cardiovascular disease.

### 8. Future pharmacological approaches to lowering remnant cholesterol levels

Given the documented causal association between elevated levels of remnant cholesterol and increased risk of IHD (Jorgensen et al., 2013; Varbo et al., 2013a; Varbo et al., 2013b), and the lack of well documented effect in reducing IHD risk in those with elevated remnant cholesterol levels with statins, fibrates, and/or niacin, there is a clear need for new therapies to reduce remnant cholesterol as add on therapy to statins or to be used in statin intolerant patients.

One possibility is to use omega-3 fatty acids, or fish oil, to lower remnant cholesterol levels, although the use of such drugs have so far focused on lowering triglycerides to reduce risk of pancreatitis in those with triglycerides >5 mmol/L (440 mg/dL). However, recent trials have suggested that some omega-3 fatty acids may also reduce remnant cholesterol levels (Bays et al., 2012), but large randomized trials to detect reduced IHD risk after such treatment is awaited. So far randomized clinical intervention trials with fish oil in secondary prevention of...
cardiovascular disease have had conflicting results (Casula et al., 2013; Kwak et al., 2012; Rizos et al., 2012).

Other possibilities include a large number of novel drugs in the process of being developed and tested for clinical use (Gotto & Moon, 2013). These include drugs targeting the production of apolipoprotein B with the APOB antisense oligonucleotide mipomersen (Raal et al., 2010), recently approved for use in patients with homozygous familial hypercholesterolemia in the US, and the MTP inhibitor lomitapide (Cuchel et al., 2007; Cuchel et al., 2013), also recently approved for use in patients with homozygous familial hypercholesterolemia, in the US and in Europe. Both mipomersen and lomitapide unfortunately have adverse effects including increasing hepatic lipid content, which so far limits the use to add on therapy to other lipid-lowering therapies in patients with homozygous familial hypercholesterolemia.

Another new line of drugs being developed are antibodies against plasma proprotein convertase subtilisin/kexin type 9 (PCSK9) (Lee & Hegele, 2013). PCSK9 binds to the LDL receptor and promotes its degradation, and inhibition of PCSK9 increases the number of LDL receptors on the liver, promoting LDL uptake from plasma, and possibly also uptake of remnants. Also, antisense inhibition of APOC3, encoding apolipoprotein C3, have in preclinical models and in a phase I clinical trial showed promising results regarding reduction of triglyceride levels (Graham et al., 2013). There has also been developed gene therapy for lipoprotein lipase deficiency, which has been shown to lower triglycerides in patients with severe hypertriglyceridemia (Gaudet et al., 2012), and are now approved for clinical use in Europe; lipoprotein lipase activators are likewise being developed (Eriksson et al., 2013). Finally, several drugs that inhibit CETP have been developed; however, results so far have either showed increased risk of cardiovascular disease of CETP inhibition on top of statins (Barter et al., 2007), or no effect on risk of cardiovascular disease (Schwartz et al., 2012), compared to statin therapy alone. Results from two additional randomized clinical intervention trials are awaited (Cannon et al., 2010; Nicholls et al., 2011).

Importantly, before any of these novel therapies, potentially to be used to lower remnant cholesterol/triglyceride levels, can reach clinical use, they need to be documented to be efficacious in reducing remnant cholesterol levels, to be largely free of side effects, and eventually to be shown to reduce risk of cardiovascular disease, either as an add on to statin therapy or by themselves in statin intolerant patients.

9. Conclusions and perspectives

In conclusion, evidence from observational studies, in-vitro and animal studies, and from genetic studies all support a common association between elevated levels of remnant cholesterol and increased risk of IHD; however, even though post-hoc subgroup analyses of randomized trials using fibrates showed a benefit of lowering triglycerides or remnant cholesterol levels, large randomized clinical intervention trials with the primary target of lowering remnant cholesterol levels are still missing. Such positive trials may open the possibility for further reducing risk of IHD in many millions of high risk individuals worldwide.

References


